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SYSTEMATIC REVIEW

Functional and structural brain abnormalities in substance use disorder: A multimodal meta-analysis of neuroimaging studies

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Abstract

Introduction: Numerous neuroimaging studies of resting-state functional imaging and voxel-based morphometry (VBM) have revealed that patients with substance use disorder (SUD) may present brain abnormalities, but their results were inconsistent. This multimodal neuroimaging meta-analysis aimed to estimate common and specific alterations in SUD patients by combining information from all available studies of spontaneous functional activity and gray matter volume (GMV).

Methods: A whole-brain meta-analysis on resting-state functional imaging and VBM studies was conducted using the Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI) software, followed by multimodal overlapping to comprehensively investigate function and structure of the brain in SUD.

Results: In this meta-analysis, 39 independent studies with 47 datasets related to resting-state functional brain activity (1444 SUD patients; 1446 healthy controls [HCs]) were included, as well as 77 studies with 89 datasets for GMV (3457 SUD patients; 3774 HCs). Patients with SUD showed the decreased resting-state functional brain activity in the bilateral anterior cingulate cortex/medial prefrontal cortex (ACC/mPFC). For the VBM meta-analysis, patients with SUD showed the reduced GMV in the bilateral ACC/mPFC, insula, thalamus extending to striatum, and left sensorimotor cortex.

Conclusions: This multimodal meta-analysis exhibited that SUD shows common impairment in both function and structure in the ACC/mPFC, suggesting that the deficits in functional and structural domains could be correlated together. In addition, a few regions exhibited only structural impairment in SUD, including the insula, thalamus, striatum, and sensorimotor areas.

KEYWORDS

addiction, multimodal, resting-state functional imaging, substance use disorder, voxel-based morphometry

Hong Yan and Shu Xiao contributed equally to this work.

1 | INTRODUCTION

Substance use disorder (SUD) is a medical condition that is defined by the inability to control the use of a particular substance, and it is characterized by compulsive drug-seeking, loss of control in limiting intake, and the emergence of negative emotional states during withdrawal.[1] Disorders related to the consumption of alcohol, cannabis, opioids (e.g., heroin), nicotine, and stimulants (e.g., cocaine) are among the most common SUDs. Nowadays, SUD has been a major public health concern, imposing a huge global socioeconomic burden.[2] Globally, alcohol use disorder was reported as the most prevalent type of SUD diagnoses, accounting for 100.4 million cases in 2016, while the most common drug use disorders were cannabis dependence (22.1 million cases) and opioid dependence (26.8 million cases).[3] Regrettably, a limited number of therapeutic strategies with a moderate efficiency have been reported for SUD, and the rates of mortality and relapse were noticeable.[4,5] Providing new insights into the pathophysiological mechanism of SUD is therefore crucial for the development of more rational diagnostic and therapeutic approaches.

Over the past three decades, in vivo and non-invasive brain imaging techniques have been widely used to identify the neuroplastic impairment in SUDs. Luijten et al. conducted a task-based meta-analysis for addiction and found hypoactivity in the striatum, anterior cingulate cortex (ACC), and thalamus during reward anticipation, while they identified hyperactivity in the ventral striatum and insula during reward outcome.[6] Another meta-analysis performed by Klugah-Brown et al. revealed that SUD patients showed pronounced neurofunctional alterations in the frontal lobe during cognitive tasks, while stronger functional alterations were detected in the reward system during reward task paradigms.[7] Experimental paradigm can cause variations in neural reactivity due to study-specific factors, such as targeted sensory modality or the type and length of cue presentation in reactivity processes.[8] Resting-state functional imaging provides a task-free approach that may avoid heterogeneity during the differences of experimental design and performance of the complicated tasks. Therefore, we focused on resting-state functional imaging to reflect spontaneous neural activity.[9] Two primary consequences of the increased neural activity are changes in oxygenation concentration (blood-oxygen-level-dependent [BOLD][10] signal) and regional cerebral blood flow (CBF).[11] The former consists of three local metrics, which can be measured by functional magnetic resonance imaging (fMRI), including regional homogeneity (ReHo), amplitude of low-frequency fluctuation (ALFF), and its standardized variant of the fractional ALFF (fALFF). ReHo reflects the time-series similarity of BOLD signals of a given voxel with its nearest neighbors.[12] ALFF and fALFF examine the strength of BOLD signal oscillations within a specific low-frequency range (0.01–0.08 Hz) at the single-voxel level.[13,14] Moreover, CBF can be quantified by fMRI, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) using endogenous arterial water (arterial spin labeling [ASL][15]) or exogenous radioisotopes. Previous resting-state functional imaging studies revealed the increased spontaneous brain activity in the ACC,[16] thalamus,[17] and striatum[18] of SUD patients, while other studies reported a decrease in the ACC,[19,20] thalamus,[21] and striatum[22] of such patients. This inconsistency may be attributed to the different definitions of SUD, types of substances, duration of substance use, phase of addiction, and technical procedures. Meta-analysis is a potent approach for synthesizing inconsistent findings by accounting for between-study heterogeneities.[23] Several meta-analyses of neuroimaging studies indicated that it is practicable to pool various resting-state functional metrics together that can provide a more systematic assessment of brain dysfunction.[24–26] Of late, only one meta-analysis of resting-state functional

Summations

- Resting-state functional activity was reduced in the bilateral ACC/mPFC of SUD patients.
- GMV decreased in the bilateral ACC/mPFC, insula, thalamus extending to striatum, and left sensorimotor areas of SUD patients.
- SUD shows common impairment in both function and structure in the ACC/mPFC. The ACC/mPFC may provide potential therapeutic targets for addictive drugs-induced brain injury.

Limitations

- Data were based on coordinates frompublished studies rather than raw statistical brain maps.
- It was infeasible to determine whether thefunctional and anatomic alterations are parts of the pathogenesis of SUD orconsequences of the disease.
- This study did not directly detectcorrelations between functional and structural abnormalities, while showed thatbrain regions in SUD patients were associated with functional and structuralchanges.

connectivity showed hyperconnectivity in the amygdala-basal ganglia, thalamus-midbrain and hypoconnectivity in the posterior lobe in addiction.[27] However, local spontaneous neural activity cannot be addressed using these approaches.

Apart from functional abnormalities, morphological brain changes of patients with SUD were found in previous structural MRI studies. Voxel-based morphometry (VBM) is an automatic whole-brain method that can calculate the regional gray matter volume (GMV) in an unbiased manner. A recent VBM-based meta-analysis enrolled adult and older SUD patients (60 articles; 2429 SUD patients and 2509 healthy controls [HCs]) indicated a lower GMV in the ACC, insula, and thalamus, while a higher GMV was found in the putamen.[28] Another VBM-based meta-analysis for patients with SUD including behavioral addiction and adolescents (59 articles; 2096 SUD patients and 2637 HCs), demonstrated a lower volume in the ACC extending to medial prefrontal cortex (mPFC) and orbitofrontal cortex, insula and superior temporal gyrus, while an increased GMV in the lingual gyrus and fusiform gyrus was detected.[29] Given that several VBM-based studies have been performed in recent years[30–35] and some VBM-based studies were not included in the earlier meta-analyses,[35–45] it is necessary to carry out an updated meta-analysis to expand and/or modify the previous findings.

It is noteworthy that functional and structural brain changes are relevant, and the conjoint abnormalities of function and structure were well documented across neuropsychiatric diseases.[46–50] Hence, the present study aimed to investigate the co-localization of disease effects on SUD. For this purpose, we first performed separate meta-analyses comparing SUD patients and HCs in resting-state function and GMV alterations using the software Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI), followed by multimodal overlapping to comprehensively investigate function and structure of the brain. SDM-PSI is a new generation algorithm for coordinate-based meta-analysis, accompanying by significant improvements over traditional methods (e.g., the previous versions of SDM [AES-SDM], Activation Likelihood Estimation [ALE], and Multilevel Kernel Density Analysis [MKDA]), such as use of standard voxel-wise tests, standard permutation of subject images, unbiased estimation of effect sizes based on MetaNSUE[51] algorithms, random-effects models, Freedman-Lane-based permutations, and threshold-free cluster enhancement statistics.[52] Furthermore, we conducted subgroup meta-analyses by substance categories (alcohol, nicotine, opioids, stimulants, and cannabis), addiction phase (active use and abstinence) and imaging techniques (ReHo and ALFF) to estimate the heterogeneity and robustness of the main findings. Finally, we executed meta-regression analyses to explore the associations between the imaging results and clinical variables (age, gender, duration of substance use, and severity of symptoms). According to the previous empirical studies, it was assumed that functional and structural changes in SUD would be primarily located in the brain regions related to reward and cognitive processing, such as the ACC, prefrontal cortex, insula and striatum.

2 | METHODS

2.1 | Literature Search

This meta-analysis conforms to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. The study is registered with PROSPERO (registration number: CRD42021260285).

We searched for neuroimaging experiments in SUD using PubMed, Web of Science, Embase, SinoMed, Chinese National Knowledge Infrastructure, and WanFang through November 25, 2021, with the following MeSH terms and their derivatives: ("substance abuse" OR "substance dependence" OR "addiction" OR "substance use disorder" OR "alcohol" OR "ethanol" OR "cannabis" OR "marijuana" OR "nicotine" OR "tobacco" OR "cigarette" OR "smoker" OR "opioid" OR "opiate" OR "opium" OR "heroin" OR "morphine" OR "codeine" OR "methadone" OR "stimulant" OR "cocaine" OR "amphetamine" OR "methamphetamine" OR "ecstasy" OR "hallucinogen") AND ("neuroimaging" OR "fMRI" OR "resting-state" OR "regional homogeneity" OR "ReHo" OR "amplitude of low-frequency fluctuation" OR "ALFF" OR "fractional ALFF" OR "fALFF" OR "cerebral blood flow" OR "CBF" OR "positron emission tomography" OR "PET" OR "single photon emission computed tomography" OR "SPECT" OR "arterial spin labeling" OR "ASL" OR "Voxel-based morphometry" OR "VBM" OR "gray matter volume" OR "GMV"). Further relevant studies were identified by screening of bibliographies of retrieved articles.

2.2 | Study selection

A study meeting the following conditions was included in the meta-analysis. (1) Human adults (18–60 years of age); (2) A formal diagnosis of SUD according to DSM, ICD criteria or other objective laboratory or clinical assessment (e.g., urine drug test); (3) They compared regional resting-state functional activity or GMV between SUD patients and HCs; (4) A whole-brain analysis reported peak coordinates in stereotactic space (Montreal

Neurological Institute [MNI] or Talairach); and (5) A published peer-reviewed manuscript reported in English or Chinese.

Exclusion criteria were (1) Behavioral addiction (e.g., gambling disorder); (2) Recreational substance users or at-risk groups (e.g., addicted family members); (3) Target population with organic brain diseases, neurological diseases, and any medical condition affecting brain functioning; (4) No baseline comparison for longitudinal or intervention trials; (5) Data could not be retrieved (e.g., missing neuroanatomical coordinates); (6) Region-of-interest approach or partial brain coverage; (7) In cases where the potential target population overlapped, the study with the largest sample or higher quality was selected. Poly-SUDs or psychiatric comorbidities, as long as SUD was the primary diagnosis, were allowed for our meta-analysis.

2.3 | Data extraction

Peak coordinates and effect sizes (e.g., *t* values) of significant differences between SUD and HCs were extracted from each study. Demographic, clinical, and imaging characteristics were also obtained, including sample size, age, gender, diagnostic criteria, substance categories (e.g., alcohol, nicotine, opioids, stimulants, and cannabis), addiction phase (active use or abstinence), illness duration, symptom severity (e.g., the score of Alcohol Use Disorders Identification Test [AUDIT], Fagerström Test for Nicotine Dependence [FTND], Barratt Impulsiveness Scale [BIS]), scanner, software, threshold of statistics.

2.4 | Quality assessment

We used a 10-point checklist (Table S18) to assess the study quality based on previous meta-analyses.[53,54] The checklist focused on both the clinical and demographic aspects of individual study samples and on the imaging-specific methodology.[54]

Two investigators (H.Y. and S.Y.F.) independently screened titles and abstracts, full-text articles, extracted data, and assessed the quality of all included studies. An independent third investigator (J.Y.G.) adjudicated on disagreements.

2.5 | Voxel-wise meta-analysis

Separate meta-analyses of regional brain activity and GMV abnormalities were performed using the software of Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI, version 6.21) in a standard process (www.sdmproject.com). In brief, peak coordinates and effect sizes are entered to impute, for each study, multiple effect size maps of contrast results. MetaNSUE is applied to estimate the maximum likely effect size and adds realistic noise. The maps are then consolidated in a standard random-effects model weighing sample size, intra-study variability, and between-study heterogeneity, and multiple imputations are pooled according to Rubin's rules. Finally, a subject-based permutation test is applied to calculate the familywise error rate of the results.[51,52,55]

We used the default recommended parameters (full width at half maximum [FWHM] = 20 mm, mask = gray matter) for pre-processing, 1000 permutations for familywise error (FWE) correction, a threshold-free cluster enhancement (TFCE) corrected $p = 0.05$ for determination of significant effects and visualized SDM maps with MRIcron software (www.mricro.com/mricron/).

2.6 | Multimodal meta-analysis

The co-location of functional and structural abnormalities in SUD was investigated by overlapping thresholded meta-analytic results-maps of resting-state functional activity and GMV alterations to examine convergence in results from different modalities.

2.7 | Subgroup analysis

To investigate underlying clinical and methodological heterogeneity, we redid the meta-analyses in the following subgroups: substance categories (alcohol, nicotine, opioids, stimulants and cannabis), addiction phase (active use and abstinence), and imaging techniques (ReHo and ALFF). Furthermore, the confirmatory subgroup analyses were carried out when excluding studies of SUD patients with psychiatric comorbidities, as well as were carried out when excluding studies of insufficient subjects ($n < 10$) or uncorrected for multiple comparisons.

2.8 | Jackknife sensitivity analysis

To examine the robustness of the findings, we conducted a jackknife analysis by iteratively repeating the meta-analyses and removing one study at a time. This process has been extensively used in quantitative

meta-analyses of neuroimaging data.[56–59] Brain regions that remain significant in all or most of the study combinations likely have a high degree of replicability.

2.9 | Analysis of heterogeneity and publication bias

Between-study heterogeneity was tested with the I^2 statistic, where $I^2 < 50\%$ commonly indicates low heterogeneity. Potential publication bias was evaluated by Egger's tests and visual inspection of the symmetry in funnel plots. Egger's $P < 0.05$ and an asymmetric plot were suggested a significant bias of publication.

2.10 | Meta-regression analysis

To explore the associations between the meta-analysis results and clinical variables (including age, gender, duration of substance use, and severity of symptoms), we executed meta-regression analyses within the SUD. A more conservative threshold was set at $p < 0.05$, TFCE-FWE corrected, to avoid reporting spurious relationships.[59–61] Abnormalities were needed to be detected both in the slope and in one of the extremes of the regressor and findings in regions other than those identified in the main analyses were discarded.

3 | RESULTS

3.1 | Included studies and sample characteristics

We included 39 studies (47 datasets) for resting-state functional brain activity and 77 studies (89 datasets) for GMV (Figure 1). The functional meta-analysis comprised a total of 1444 SUD patients (mean age = 34.9 years, 88.1% males) and 1446 healthy controls (mean age = 34.8 years, 86.4% males). Groups did not differ on age ($t = 0.066$, $p = 0.947$) or gender ($\chi 2 = 1.746$, $p = 0.168$). Of the patients with SUD, 27.6% were opioid use disorder (16 datasets), 26.5% were nicotine use disorder (9 datasets), 24.5% were stimulant use disorder (10 datasets), 12.5% were alcohol use disorder (7 datasets), and 8.9% were another type or unspecified. Of all these patients, 39.4% were active drug users (18 datasets), 49.7% were abstinent (23 datasets), and 10.9% were unspecified. Specific to resting-state functional activity, 22 publications (22 datasets) examined ReHo, 14 publications (16 datasets) examined ALFF, 6 publications (6 datasets) examined fALFF, 3 publications (4 datasets) examined CBF.

The structural meta-analysis comprised a total of 3457 SUD patients (mean age = 37.9 years, 77.8% males) and 3767 healthy controls (mean age = 38.6, 71.8% males). Groups did not differ on age ($t = 0.948$, $p = 0.345$) but differ on gender ($\chi 2 = 33.032$, $p = 0.001$). Of the patients with SUD, 26.2% were nicotine use disorder (16 datasets), 25.5% were stimulant use disorder (21 datasets), 22.4% were alcohol use disorder (20 datasets), 10.5% were opioid use disorder (15 datasets), 5.1% were cannabis use disorder (7 datasets), and 10.3% were another type or unspecified. Of all these patients, 31.8% were active drug users (22 datasets), 45.7% were abstinent (41 datasets), 4.2% received methadone maintenance treatment (6 datasets), and 18.3% were unspecified.

The demographic, clinical, imaging characteristics, and quality score of the included studies are presented in Tables S1 and S2.

3.2 | Voxel-wise meta-analysis

Patients with SUD showed decreased resting-state functional activity in the bilateral ACC extending to medial prefrontal cortex (mPFC), compared to HCs. No significantly increased resting-state functional activity was observed in patients with SUD. See Figure 2A and Table 1.

Patients with SUD showed decreased GMV in the bilateral ACC/mPFC and middle cingulate cortex, bilateral insula, bilateral thalamus extending to striatum, and left postcentral gyrus, compared to HCs. No significantly increased GMV was observed in patients with SUD. See Figure 2B and Table 2.

3.3 | Multimodal meta-analysis

Patients with SUD showed a conjoint decrease of intrinsic functional activity and regional GMV in the bilateral ACC extending to mPFC, compared to HCs. See Figure 2C and Table 3.

3.4 | Subgroup analysis

Samples size of subgroup meta-analyses are presented in Table S3. In the subgroup analysis of different types of substances, for resting-state functional activity, patients with opioid use disorder displayed hypoactivity in the bilateral

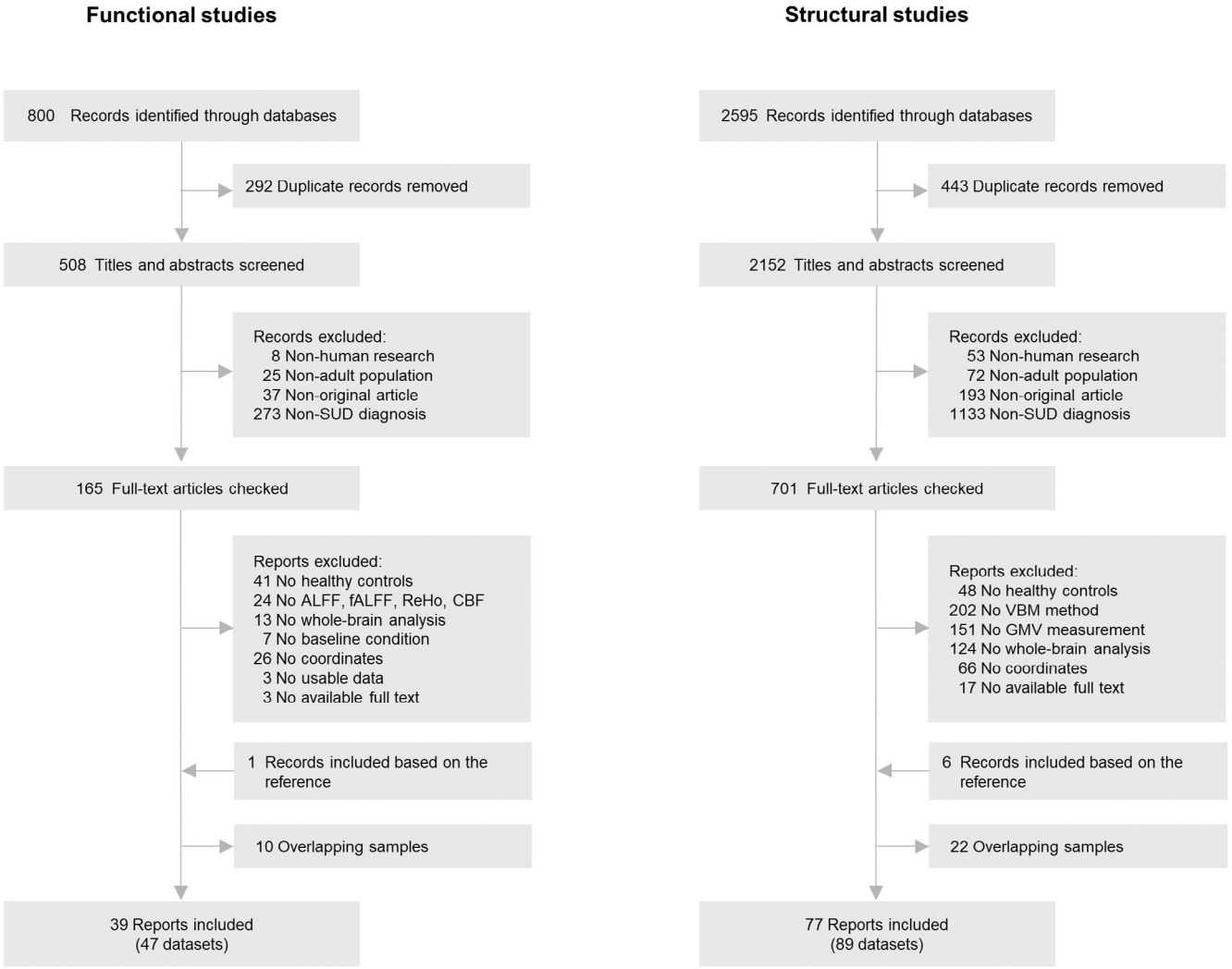

FIGURE 1 Flow chart of meta-analysis of resting-state functional imaging and VBM studies of patients with SUD. Abbreviations: SUD, substance use disorder; ALFF, amplitude of low-frequency signal fluctuations; fALFF, fractional amplitude of low-frequency signal fluctuations; ReHo, regional homogeneity; CBF, cerebral blood flow; VBM, voxel-based morphometry; GMV, gray matter volume.

ACC/mPFC, and hyperactivity in the left cerebellum, and patients with stimulant use disorder showed hypoactivity in the right postcentral gyrus; for GMV, patients with opioid use disorder displayed decreased GMV in the bilateral ACC/mPFC, and patients with alcohol use disorder showed decreased GMV in the anterior and middle cingulate cortex, bilateral insula, left postcentral gyrus, and right precentral gyrus. Patients with nicotine or stimulant use disorder showed no significant differences compared with HCs. Additionally, datasets were inadequate ($n < 10$) to complete subgroup analyses on other types of substances. See supplementary materials Figure S1 and Tables S4–S7.

During abstinence, patients with SUD showed hypoactivity in the bilateral ACC/mPFC and decreased GMV in the bilateral ACC/mPFC, bilateral insula, bilateral thalamus, and the left postcentral gyrus. For the subgroup of active use phase, patients with SUD showed no significant differences in resting-state functional activity or GMV compared with HCs. See supplementary materials (Figure S2 and Tables S8–S9).

Besides, the results of subgroup analysis on SUD patients without psychiatric comorbidities were generally consistent with our main results. Specifically, for resting-state functional brain activity analysis (32 studies with 37 datasets), patients with SUD showed hypoactivity in the bilateral ACC/mPFC; for GMV analysis (60 studies with 69 datasets), patients with SUD displayed the reduced GMV in the bilateral ACC/mPFC and middle cingulate cortex, right insula, bilateral thalamus, left postcentral gyrus, and left superior temporal gyrus. See supplementary materials Figure S3 and Tables S10–S11.

To explore the potential effects of different functional imaging methodologies, we performed subgroup analysis of ReHo, which indicated hypoactivity in the bilateral

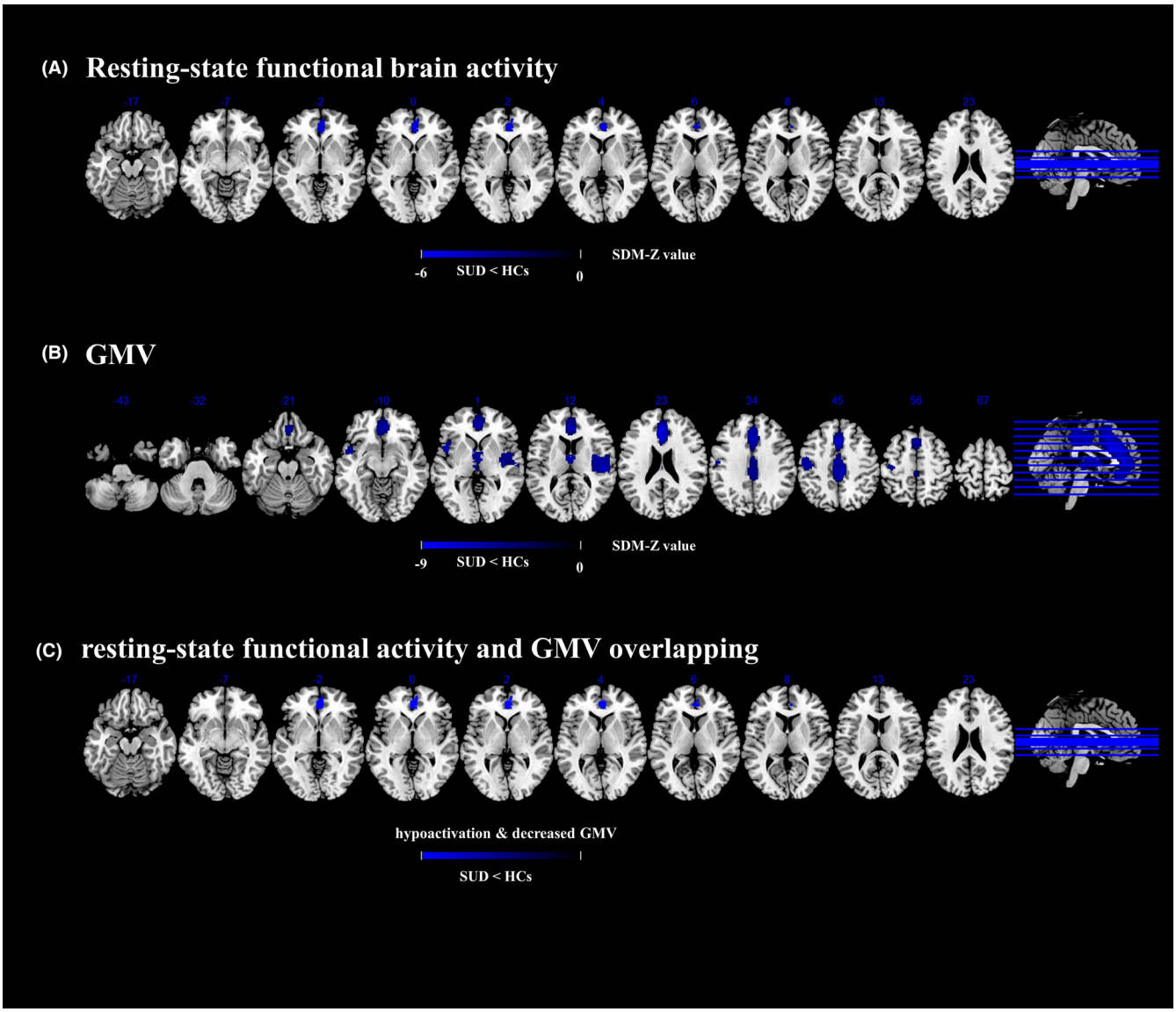

FIGURE 2 A meta-analysis of resting-state functional brain activity and GMV alterations in patients with SUD. Meta-analysis results regarding (A) difference of resting-state functional brain activity between patients with SUD and HCs, (B) difference of GMV between SUD and HCs, (C) Multimodal overlap of difference of resting-state functional brain activity and GMV of patients with SUD. Areas with decreased resting-state functional brain activity or GMV value are displayed in blue. The color bar indicates the maximum and minimum SDM-Z values. Abbreviations: SUD, substance use disorder; HCs, healthy controls; SDM, seed-based *d* mapping; GMV, gray matter volume.

ACC/mPFC, and analysis of ALFF revealed hypoactivity in the bilateral ACC/mPFC and hyperactivity in the left cerebellum. However, the same analysis was not carried out in fALFF and CBF subgroups because of their inadequate number of datasets. See supplementary materials Figure S4 and Tables S12–S13.

Finally, subgroup analysis was conducted on excluding studies of insufficient subjects ($n < 10$) or uncorrected for statistics, which also validated our main results. Specifically, for resting-state functional brain activity analysis (28 studies with 36 datasets), patients with SUD showed hypoactivity in the bilateral ACC/mPFC; for GMV analysis (57 studies with 68 datasets), patients with SUD displayed the reduced GMV in the bilateral ACC/mPFC and middle cingulate cortex, bilateral insula, bilateral thalamus, and left postcentral gyrus. See supplementary materials Figure S5 and Tables S14–S15.

3.5 | Jackknife sensitivity analysis

In the meta-analysis of resting-state functional brain activity, jackknife sensitivity analysis showed that

TABLE 1 Meta-analysis results of regional resting-state functional brain activity in SUD compared with HCs.

Local maximum				Cluster			
Region	Peak MNI coordinate (x, y, z)	SDM-Z value	*p* value	No. of voxels	Breakdown (No. of voxels)	I^2	Egger's test (*p* value)
SUD < HCs							
R anterior cingulate/paracingulate gyri, BA 10	2,42,2	−5.260	0.005	239	R anterior cingulate/paracingulate gyri, BAs 10, 11, 25, 32 (93) L anterior cingulate/paracingulate gyri, BAs 10, 11, 25, 32 (69) R superior frontal gyrus, medial, BA 10(68) L superior frontal gyrus, medial, BA 10(4)	1.725	0.695

Abbreviations: BA, Brodmann area; HCs, healthy controls; L, left; MNI, Montreal Neurological Institute; R, right; SDM, seed-based d mapping; SUD, substance use disorder.

hypoactivity in the bilateral ACC/mPFC was preserved throughout all study combinations.

In the meta-analysis of structural studies, jackknife sensitivity analysis showed the decreased GMV in the bilateral ACC/mPFC extending to middle cingulate cortex, bilateral insula, bilateral thalamus extending to striatum, and the left postcentral gyrus remained significant in all combinations.

The results of the functional and structural meta-analyses showed high replicability and reliability.

3.6 | Analysis of heterogeneity and publication bias

Both in regional function and VBM-based meta-analyses, none of the brain regions with altered function and structure showed significant heterogeneity ($I^2 < 50\%$) and publication bias (Egger's test, $p > 0.05$) among the included studies. See supplementary materials, Tables S16–S17.

3.7 | Meta-regression analysis

Meta-regression analysis showed no significant associations between the altered resting-state functional activity or regional GMV and clinical measurements (age, percentage of male participants, duration of substance use, and severity of illness score).

4 | DISCUSSION

To the best of our knowledge, this is the first and largest multimodal neuroimaging meta-analysis that combines information from whole-brain voxel-based studies, investigating resting-state functional activity and GMV, in order to more consistently localize the neural substrates of the SUD. The main findings of the present meta-analysis were summarized as follows: (a) Resting-state functional activity was reduced in the bilateral ACC/mPFC of SUD patients. (b) GMV decreased in the bilateral ACC/mPFC, insula, thalamus extending to striatum, and left sensorimotor areas of SUD patients. (c) Functional and structural reductions overlapped in the bilateral ACC/mPFC of SUD patients. (d) The findings of subgroup analysis of SUD patients without psychiatric comorbidities were generally consistent with our main results. The findings of subgroup analysis of different functional imaging modalities (i.e., ALFF and ReHo) and analytical procedures (i.e., excluding studies of insufficient subjects [$n < 10$] or uncorrected for statistics) were also similar to our main results. In addition, the main functional activity and structural changes in SUD remained unaffected by the potential confounding variables of age, gender, duration of substance use, and severity of symptoms, further confirming the robustness of the findings.

Identification of a consistent decrease in spontaneous neural activity and GMV in the ACC/mPFC in our meta-analysis was a potentially significant finding for SUD, suggesting that functional impairment might be associated with structural deficits. Additionally, deficits in the ACC/mPFC were also found in the subgroup analysis of substance types of alcohol (GMV) and opioids (resting-state functional brain activity and GMV), indicating that lesion of the ACC/mPFC could be the common physiopathology in SUD among various types of substances. Furthermore, spontaneous neural activity and GMV were reduced in the ACC/mPFC in abstinent patients with SUD rather than in active drug users. The ACC/mPFC has been widely implicated in SUD, playing a crucial role in cognitive control (i.e., the ability to orchestrate thought and action in accordance with internal goals),

TABLE 2 Meta-analysis results of regional GMV in SUD compared with HCs.

Local maximum				Cluster			
Region	Peak MNI coordinate (x, y, z)	SDM-Z value	*p* value	No. of voxels	Breakdown (No. of voxels)	I^2	Egger's test (*p* value)
SUD < HCs							
L anterior cingulate/paracingulate gyri, BA 24	−4, 28, 28	−8.547	0.001	5577	L anterior cingulate/paracingulate gyri, BAs 10, 11, 24, 25, 32 (884) R anterior cingulate/paracingulate gyri, BAs 10, 11, 24, 25, 32 (541) R median cingulate/paracingulate gyri, BAs 4, 9, 23, 24, 32 (953) L median cingulate/paracingulate gyri, BAs 23, 24, 32 (777) L superior frontal gyrus, medial, BA 8, 9, 10, 11, 24, 32 (698) R superior frontal gyrus, medial, BAs 8, 9, 10, 11, 32 (502) L supplementary motor area, BA 4, 6, 8, 23, 24, 32 (391) L gyrus rectus, BA 11 (107) R gyrus rectus, BA 11 (94) R supplementary motor area, BAs 4, 6, 8, 24, 32 (194) L paracentral lobule, BA 4 (76) R paracentral lobule, BA 4 (26) L posterior cingulate gyrus, BA 23 (14) R precuneus (8) L gyrus rectus (6) R posterior cingulate gyrus, BA 23 (1)	5.264	0.636
R insula, BA 48	38, −4, 6	−6.973	0.001	1673	R insula, BA 48 (474) R rolandic operculum, BAs 42, 48 (466) R superior temporal gyrus, BAs 22, 42, 48 (229) R heschl gyrus, BA 48 (165) R lenticular nucleus, putamen, BA 48 (55) R supramarginal gyrus, BAs 42, 48 (19)	3.032	0.849
R thalamus	4, −8, 10	−6.521	0.002	696	L thalamus (111) R thalamus (47) L caudate nucleus, BA 25 (18) L striatum (3)	29.361	0.405
L postcentral gyrus, BA 4	−50, −16, 42	−6.198	0.002	474	L postcentral gyrus, BA 3, 4, 6, 43 (402) L precentral gyrus, BA 4, 6 (58) L inferior parietal (excluding supramarginal and angular) gyri, BA 3 (6) L supramarginal gyrus, BA 3 (3)	48.531	0.866
L insula, BA 48	−42, 16, 2	−5.417	0.004	345	L insula, BAs 45, 48 (76) L inferior frontal gyrus, BAs 6, 45, 47, 48 (70) L superior temporal gyrus, BAs 21, 38, 48 (72) L rolandic operculum, BA 48 (30) L temporal pole, superior temporal gyrus, BAs 38, 48 (65)	0.248	0.922

Abbreviations: BA, Brodmann area; HCs, healthy controls; L, left; MNI, Montreal Neurological Institute; R, right; SDM, seed-based d mapping; SUD, substance use disorder.

TABLE 3 Multimodally affected brain regions in SUD.

Local maximum Region	Cluster No. of voxels	Breakdown (No. of voxels)
Hypoactivity and decreased GMV		
B anterior cingulate/ paracingulate gyri	224	R anterior cingulate/ paracingulate gyri (82)
		L anterior cingulate/ paracingulate gyri (67)
		R superior frontal gyrus, medial (68)
		L superior frontal gyrus, medial (4)

Abbreviations: B, bilateral; L, left; MNI, Montreal Neurological Institute; R, right; SUD, substance use disorder.

reward processing, and decision-making.[6,62,63] Functional and structural disruption of the ACC/mPFC may partly explain impulsive choice related to increased preference for immediate rewards rather than beneficial delayed rewards in patients with SUD.[64] Thus, SUD is characterized by compulsive and persistent drug-seeking and drug-taking behaviors despite serious negative consequences. Furthermore, substantial evidence from clinical and animal studies suggested that axonal arbors of neurons were destroyed and concentration of glutamate (whose neurotransmission is fundamental to brain function) were reduced in the ACC/mPFC of SUD patients.[65,66] Particularly, randomized longitudinal prospective studies on non-human primates inferred a causal relationship that chronic use of drugs might cause prefrontal cortex damage, which was consistent with the results of human neurobiological studies.[67] Recent studies have reported that transcranial magnetic stimulation of the ACC/mPFC could reduce drug craving and self-administration in SUD patients.[68,69] Taking together, the ACC/mPFC may provide potential therapeutic targets for addictive drugs-induced brain injury.

Specific to structure only, decreased GMV in the bilateral insula was detected in SUD patients, suggesting damage to the insula in such patients. These findings were broadly consistent with those of previous structural meta-analyses.[28,70] In the subgroup analysis, the structural disruption of the insula was found in patients with alcohol use disorder. The insula serves as a receiver and interpreter of emotions in the context of cognitive and sensory-motor information.[71,72] A meta-analysis of task-based fMRI studies showed that lesions of the insula in SUD patients could produce disadvantageous choices on monetary tasks that model real-life decisions.[73] Cumulative evidence suggested that disruption of the insula in SUD may underline a dysfunction in interoceptive and somatic states processing, as well as alterations of visceral and homeostatic processes, which may elicit the need to drugs, change emotional response, promote failure in decision-making and loss of control, and further contribute to the onset and maintenance of addiction.[74,75] The insula contains a high concentration and a high density of receptors (e.g., glutamate receptor, serotonergic receptor, and norepinephrine receptor) that can bind to addictive drugs. In addition, data from postmortem and animal models indicated that relapsed drug-taking may cause neurotoxicity by binding to the corresponding receptors, which may further impair the insular neurons and lead to neuronal necrosis and synaptic alteration.[76–79] These insular substrates may help account for the behavior of SUD, and structural impairment in the insula may be a key neurobiological feature of SUD.

In the present study, it was found GMV reduction in the bilateral thalamus extending to striatum in SUD, indicating the anatomical disruption of the thalamus and striatum in SUD patients. A previous structural meta-analysis with a relatively small sample size (9 studies with 296 subjects) also reported the reduced GMV in the striatum of SUD patients.[80] Although regions of striatum play a dominant role in the current reward theories in addiction, their function in isolation is insignificant. The regions of striatum and thalamus constitute cortico-striatal-thalamo-cortical circuitry underlying both reward behaviors and executive control process.[81,82] Specifically, the thalamus, as both input and output components within this circuit, and working as a relay between orbitofrontal cortex and nucleus accumbens (a key node of the striatum), has a role in coordinating, integrating, encoding, and planning,[83,84] while the striatum is critically engaged in reward response.[85] The striatum receives major dopaminergic projections from the cortex, primarily the ACC/mPFC, and it projects to the thalamus via the globus pallidus, which then projects back to the ACC/mPFC.[84,86] Previous magnetic resonance spectroscopy (MRS) studies have found the decreased thalamic and striatal N-acetyl aspartate levels, a putative marker for neuronal viability, in SUD.[87] Evidence from prior studies showed that lesions of this circuit would lead to increase craving for addictive drugs and shorten abstinence length and duration of substance use.[86,88,89] Given that the thalamus and striatum both play a crucial role in reward prediction and have a reciprocal influence on activity of each other, future work should concentrate on this circuitry in the context of reward processing in SUD.

Moreover, decreased GMV in the right postcentral and precentral gyrus belonging to sensorimotor areas was observed. Sensorimotor areas are engaged in receiving and processing sensory and motor signals to guide ongoing behaviors.[90] Behaviorally, impairment of sensorimotor areas may be responsible for habitual and compulsive

drug taking, and it is also implicated for relapse to drug seeking following abstinence or extinction.[91,92] A previous study indicated that drug abuse could impair plasticity of the sensorimotor cortex.[93] Thus, these findings suggested that deficits of postcentral and precentral gyrus could be attributed to the motor control impairment in SUD. Remarkably, the results of subgroup analysis were not completely consistent across types of substances. For the GMV, the alcohol-specific effects displayed the wider spatial distribution (i.e., bilateral sensorimotor areas, bilateral ACC/mPFC, and bilateral insula) than other types of substances in the present study. We could not have a uniform assessment of lifetime exposure to each substance. However, alcohol consumption is legal and enjoys greater cultural acceptance in the majority of countries relative to the other substances.[94] More importantly, alcohol is thought to bring directly on neurotoxicity via thiamine deficiency, acetaldehyde toxicity and neuroinflammation caused by immune system induction, leading to the acceleration of neurodegeneration more generally.[95] Overall, different substances have common and distinct morphological pathology, suggesting that different physiopathological and therapeutic approaches should be considered for SUD patients in the future research.

Interestingly, more regions were found structurally altered than functionally i.e., insula, thalamus, striatum, and sensorimotor cortex in patients with SUD. Several task-based fMRI meta-analyses on SUD revealed hypoactivation in the striatum and thalamus during reward-related tasks[6] and hyperactivation in the insula and sensorimotor cortex during cognitive task paradigms.[7] The brain regions structurally altered while missing changes in resting-state functional activity could prefer to respond under task loading and disclose a potential dysfunction. In addition, substance use status (i.e., active vs. abstinent) could potentially alter brain responses due to the presence/absence of the acute pharmacological effects of substances of abuse. A recent task-based fMRI meta-analysis showed hypoactivation in the ACC and middle frontal gyrus in addicted individuals with active substance use during response inhibition. In contrast, abstinent substance users did not exhibit significant activation differences.[96] However, the findings of the present study revealed reduction of GMV in the ACC/mPFC, insula, thalamus, and sensorimotor cortex, as well as the decreased resting-state functional activity in the ACC/mPFC during abstinence, while there was no significant structural or functional damage during active use. A growing body of evidence indicated that lapses after a period of abstinence could cause more serious damage to the brain than drug use during active phase in SUD patients.[97] Natural barriers of the brain become more active during drug use to partially compensate for the toxic effects of drugs, whereas after a period of abstinence, these natural biological barriers may decline and make the brain more vulnerable to the effects of drugs toxic during lapses.[98] However, a review of longitudinal neuroimaging studies demonstrated at least partially neurobiological recovery with abstinence. Moreover, the onset of structural recovery appears to precede neurochemical recovery, commencing soon after cessation (particularly for alcohol); functional recovery may require a longer period of abstinence.[99] Therefore, future meta-analysis employing multiple assessments at different time-points (e.g., longitudinal studies of different abstinence periods) and combining different functional modalities (e.g., task and resting-state fMRI) are warranted to accurately capture the recovery time spectrum in patients with SUD.

4.1 | Limitations

Firstly, as all the included studies were cross-sectional, it was infeasible to determine whether the functional and anatomic alterations are parts of the pathogenesis of SUD or consequences of the disease. Secondly, it is mainly difficult to disambiguate the pharmacological effects of a drug from the dependence-producing properties of an agent. The next research will investigate behavioral addiction where brain alterations are most likely a result of the disease itself. Thirdly, given the high prevalence of comorbidity between SUD and other mental disorders[100] but certain included studies did not provide enough information to confine other psychiatric diagnoses than SUD, we cannot rule out the effects of comorbidity on the results of the present study. Although subgroup analyses of SUD patients without comorbid psychiatric conditions were carried out that validated the main results, additional studies are required to enhance the generalizability of the result. Fourthly, as there were limited datasets, no subgroup analysis on other types of substances (e.g., alcohol, nicotine) for resting-state functional activity was conducted. Fifthly, in some studies, tobacco and alcohol exposure was not considered as covariates to adjust for potential confounding. Sixthly, this voxel-based meta-analysis was based on summarized data (e.g., stereotactic coordinates reported from published studies) rather than raw data. In addition, differences of functional imaging methodology may be potential confounders and lead to biased results, while the findings of subgroup analysis (grouped by different modalities) were broadly consistent with the main results. Finally, multimodal analysis, as conducted in this study, did not directly detect correlations between functional and structural abnormalities, while showed that brain regions in SUD patients were associated with functional and structural

changes. Future studies are encouraged to investigate the spatial and temporal relationships between the function and structure of the regions detected in this meta-analysis.

5 | CONCLUSIONS

The multimodal meta-analysis exhibited that SUD shows common impairment in both function and structure in the ACC/mPFC, suggesting that the deficits in functional and structural domains could be correlated together. In addition, a few regions exhibited only structural disruption in SUD, including the insula, thalamus, striatum, and sensorimotor areas. These lesions of spontaneous neural activity and structure may contribute to further understanding of the pathophysiology of SUD, and they may be regarded as imaging biomarkers for early diagnosis and treatment of SUDs.

AUTHOR CONTRIBUTIONS

Hong Yan and Shu Xiao contributed equally as first authors, took the whole responsibility of data collection and statistical analyses, and drafted the initial manuscript. Siying Fu, Jiaying Gong, Zhangzhang Qi, Pan Chen, Guixian Tang, Ting Su and Zibin Yang contributed to data collection and data interpretation. Ying Wang contributed as corresponding author, took the responsibility of collection of all information from the other co-authors, major revision of the manuscript, and full access to the study design and data interpretation. All authors have read and approved the final version of the submitted manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

No ethical approval was sought because data from previous studies in which informed consent was obtained by primary investigators were retrieved and analyzed.

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